REMARKS

Claims 1, 2, 5, 6, 9, 10, 12, 13, 30, 33, 34, 36, 37, 44-52, 54-60, and 62-74 were pending in this application. Claims 34, 55, 56, 69 and 70 have been amended. Accordingly, claims 1, 2, 5, 6, 9, 10, 12, 13, 30, 33, 34, 36, 37, 44-52, 54-60, and 62-74 are being examined.

Support for amended claims 34, 55, 56, 69 and 70 can be found in the specification as originally filed. Accordingly, these changes do not involve new matter and Applicants respectfully request entry of these changes.

Support for amended claims 34, 55 and 56 is found on page 51, lines 23-25 and page 50, lines 9-12, in the originally filed application.

Support for amended claims 69 and 70 can be found on page 20, lines 1-2, of the originally filed application.

ITEM 1: APPLICANTS' AMENDMENTS

The Office acknowledges the amendments filed by the Applicants on March 24, 2005, and claims 1, 2, 5, 6, 9, 10, 12, 13, 30, 33, 34, 36, 37, 44-52, 54-60 and 62-74 are pending.

No response is due.

ITEM 2: SPECIES ELECTION

The Office acknowledges the Applicants' election of the following species with traversal:

the alkylating agent is busulfan;

the first ligand is soluble CTLA4;

the second ligand is anti-CD40 antibody, and

the targeted condition is solid organ or tissue/cellular transplant.

The Office has indicated that in the interest of compact prosecution, and in view of enablement issues under 35 U.S.C. §112, first paragraph, the Office has extended the search to include another alkylating agent, cyclophosphamide, in addition to busulfan. Therefore, claims 1-6, 9-13, 17, 28-37, 44-52, 54-60 and 62-74, are being examined in the instant application, to the extent that they read on the elected species.

No response is due.

ITEM 3

The Office did not indicate which statute of title 35 USC is being cited in the outstanding Office Action. The Office also indicated that this Action is in response to Applicants' amendments filed on March 27, 2006.and the rejections of record can be found in the previous Office Action.

No response is due.

ITEM 4: PRIORITY

The Office takes the position that the filing date of the instant claims is deemed to be the filing date of priority application U.S. Serial No. 60/303,142, filed July 5, 2001 rather than priority application U.S. Serial No. 60/264,528 filed January 26, 2001.

At page 3 of the Office Action, the Office reiterates its allegation that the priority application, U.S. Serial No. 60/264,528, filed January 26, 2001, does not provide sufficient written description for

(a) "administering TDBM before, during and/or after a solid organ or tissue/cellular transplant";

(b) "subsequently administering an alkylating agent (including busulfan)"; or

(c) "administering an immunosuppressive composition before, during and/or after a solid organ tissue/cellular transplant", as currently claimed.

Applicants respectfully disagree that the priority application U.S. Serial No. 60/264,528, filed January 26, 2001, does not sufficiently describe the specific specification passages of (a)-(c) *supra* for reasons of record.

Contrary to the Office's position that parent provisional application U.S. Serial No. 60/264,528 filed January 26, 2001, only discloses a "single dose of busulfan prior to the transplantation (i.e. intravenous infusion) of T cell-depleted bone marrow cells", data supporting passages (a)-(c) *supra* can be found in said parent provisional application as follows.

Applicants' support for passage (a) ("administering TDBM before, during and/or after a solid organ or tissue/cellular transplant") may be found in the skin graft experiments, at pages 4 and 5 of U.S. Serial No. 60/264,528. These experiments clearly describe

administering TDBM on day 0 and on day 6 (page 4, line 12). The skin graft was done on day 0 (page 4, line 13). The data is shown in Figure 2A. Figure 2A clearly supports a claim of administering TDBM during and after a transplant. The claim of administering TDBM before the transplant is shown in the experiments described on pages 4-5 of U.S. Serial No. 60/264,528, in which the mice which were administered TDBM on days 0 and 6 (page 4, line 12) and were re-challenged with skin transplants 100 days after the original transplant/protocol (page 5, lines 5 and 6).

Applicants' support for passage (b) ("subsequently administering an alkylating agent")(e.g., busulfan) is in the skin graft experiments (page 4, lines 8-13 and page 2, lines 18-23) and data is shown in Figure 2 of U.S. Serial No. 60/264,528. Herein, Applicants describe using busulfan on day 5. Thus, in the skin graft experiments TDBM cells are administered on day 0, along with the skin graft, busulfan is administered on day 5, and TDBM cells are administered on day 6.

Regarding Applicants' support for passage (c) ("administering an immunosuppressive composition before, during and/or after a solid organ or tissue/cellular transplant"), the immunosuppressive composition (e.g., costimulatory blockade (CB) comprising a combination of a first ligand that interferes with binding of CD28 to either CD80 or CD86, and a second ligand that interferes with binding of CD154 to CD40), is used in the skin graft experiments described (page 4, lines 8-12 and page 2, lines 21-22) of U.S. Serial No. 60/264,528. The data is shown in Figure 2. Since the co-stimulatory blockade is described at page 2, line 22, of U.S. Serial No. 60/264,528, as being administered on days 0, 2, 4, 6, 14, and 28, the use of the terms "before, during and/or after" is appropriate.

Accordingly, U.S. Serial No. 60/264,528 support the instant claims and Applicants are entitled to the January 26, 2001 filing date. Applicants request that the Office withdraw the rejection.

ITEMS 5-6: REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The Office acknowledges Applicants' amendments to the claims filed in response to the previous Office Action have obviated the previous rejections of Claims 57, 59 and 63 under 35 U.S.C. §112, first paragraph, written description/new matter and Claims 1-6, 9-13, 17, 30, 33, 44-52, 54 and 63 under 35 U.S.C. §112, first paragraph, enablement.

No response is due.

ITEMS 7: REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

At page 4 of the outstanding Office Action, the Office acknowledges the amendments to the claims submitted in response to the previous Office Action.

At page 4 of the outstanding Office Action, the Office reiterated its rejection of claims 47-48 under 35 U.S.C. §112, first paragraph, alleging that while the specification is enabling for the specific mutant CTLA4 molecules, such as the L104EA29YIg molecule disclosed in the specification as filed, it does not reasonably provide enablement for any "CTLA4 mutant molecule," to be employed as an immunosuppressive agent in the instant claimed methods.

Applicants respectfully disagree for reasons of record.

Applicants traverse the rejection because Applicants provide methods for screening

CTLA4 mutants for their binding capacity (Example 9, pages 71-83, of the instant application). Further, Applicants provide examples of over thirty mutant molecules (Tables I and II at pages 82 and 83 and on page 70, lines 22-25), including their entire nucleotide sequences, and described the required functions for other members of the class of proteins (page 75, line 28-page 78, line 24, page 79, line 20-page 81).

35 U.S.C. § 112, first paragraph, requires Applicants to teach how to make and use the invention, without undue experimentation. The law is clear. Applicants are not required to disclose every species encompassed by the claims (*In re Angstadt and Griffin*, 537 F.2d 498, 190 USPQ 215, 218 CCPA 1976)). Moreover, despite the fact that Applicants do not disclose every known CTLA4 mutant molecule, the identification of other species in the class would not entail undue experimentation, because Applicants' disclosure outlines a number of different assays for the identification of CTLA4 mutant molecule as claimed. Practice of the claimed invention does not require undue experimentation.

In view of the preceding remarks, Applicants respectfully request that the Office reconsider and withdraw the rejection set forth in the Office Action.

ITEM 8: REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The Office acknowledges submission of Claims 65-66 and that the Applicants have satisfied the requirements under 35 U.S.C. §112, first paragraph, with the deposit of biological materials pursuant to the Budapest Treaty.

ITEM 9: REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

On page 8 of the outstanding Office Action, the office rejects Claims 67-70 under 35 U.S.C. §112, first paragraph, as containing subject matter not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In particular, the Office is requiring Applicants to provide assurance that the ATCC deposits of the biological materials be made readily obtainable to the public. Additionally, the Office is requiring the Applicants to amend the specification to recite the date of deposit and the complete name and address of the depository.

Claims 67-68 are directed to CTLA4Ig deposited as ATCC number 68629.

Claims 69-70 are directed to a cell line deposited as ATCC 10762.

The specification as originally file states at page 19, lines 27 to page 20, line 2, that "(DNA encoding CTLA4Ig was deposited on May 31, 1991 with the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, VA 20110-2209 under the provisions of the Budapest Treaty, and has been accorded ATCC accession number ATCC 68629; Linsley, P., et al., 1994 *Immunity* 1:793-80). CTLA4Ig-24, a Chinese Hamster Ovary (CHO) cell line expressing CTLA4Ig was deposited on May 31, 1991 with ATCC identification number CRL-10762)."

The originally filed specification already recites the date of deposit and the complete name and address of the depository as required by the Office. However, to further prosecution, Applicants have amended the specification to clarity that ATCC CRL-10762 was deposited with the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, VA 20110-2209 under the provisions of the Budapest Treaty.

Also, Applicants have amended Claims 69 and 70 to clarify the ATCC identification number from "ATCC 10762" to "ATCC CRL-10762".

Statement of ATCC Deposit:

Applicants' patent representative maintains that the plasmid DNA with ATCC Accession No. 68629 and the cell line with ATCC Accession No. CRL-10762 were deposited on May 31, 1991, pursuant to the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure with the Patent Culture Depository of the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, Virginia 20110-2209 U.S.A. Applicants provide a copy of the Receipt Forms issued by the American Type Culture Collection, confirming deposit of 68629 and CRL-10762 (Exhibit 1).

Accordingly, Applicants maintain that during the pendency of the present application, access to the ATCC deposits will be afforded to one determined by the Commissioner to be entitled thereto under 35 U.S.C. §1.14 and §122, and all restrictions on the availability to the public of the materials deposited under ATCC Accession Nos. 68629 and CRL-10762 will be irrevocably removed upon the issuance of a patent from the present application. Furthermore, the above deposits will be maintained by the ATCC for a period of 30 years from the date of deposit or at least 5 years after the last request for a sample of the deposited material, whichever is longer. Where the ATCC cannot furnish samples of the above deposits for any reason, Applicants shall make a replacement deposit, of the material which was originally deposited, within three months of receiving notification that the ATCC cannot furnish samples.

In view of the passage in the originally filed specification cited *supra* and the amendments to the specification and claims 69-70, Applicants respectfully request that the Patent Office reconsider and withdraw the rejection of Claims 67-70, under 35 U.S.C. §112.

ITEM 10: REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The Office acknowledges Applicants' amendments to Claim 30 filed in response to the previous Office Action have obviated the previous rejections of Claims under 35 U.S.C. §112, second paragraph.

No response is due.

ITEM 11: REJECTION UNDER 35 U.S.C. §103(a)

The Office rejects Claims 1-6, 9-13, 17, 30, 33-37, 44-52, 54-63 and 64 under 35 U.S.C §103(a), as allegedly unpatentable over Sykes et al. (U.S. Patent No. 6,514,513), in view of art known practice and modes of administration of alkylating agents such as busulfan/cyclophosmide at various times to meet the needs of the patients, as acknowledged on pages 26-27 of the instant specification as evidenced by Andersson et al. (U.S Patent Nos. 5,430,057 and 5,559,148), Hassan et al. (Blood 84,2144-2150), The Merck Manual of Diagnosis and Therapy, 17th Ed. (edited by Beers et al.), Shichi et al., (U.S. Patent No. 4,843,092), Strom et al. (Therapeutic Immunology edited by Austen et al.), Sykes et al. (Nature Medicine 3:783-787, 1997) and Wekerle et al. (J Exp Med, 187:2037-2044, 1998). The Office also cites Slattery et al (Therapeutic Drug Monitoring, 1998, 20:543-549) on page 14 of the outstanding Office Action.

Applicants respectfully disagree.

The Legal Standard for 35 U.S.C. §103

As stated in MPEP §2142, three (3) criteria must be met to establish a *prima facie* case of obviousness:

> *First*, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. *Second*, there must be a reasonable expectation of success. *Finally*, the prior art reference must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based upon applicants' disclosure.[1]

The teaching or suggestion to make the claimed combination, and the reasonable expectation of success, must both be found in the prior art, not in the Applicants' disclosure (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)).

Obviousness is a question of law based on findings of underlying facts relating to the prior art, the skill of the artisan, and objective considerations. See *Graham v. John Deere* Co., 383 U.S. 1, 17, 148 USPQ 459, 467 (1966). To establish a prima facie case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant. *In re Raynes*, 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). Obviousness can not be established by hindsight combination to produce the claimed invention. *In re Gorman*, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). As discussed in *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985), it is the prior art itself, and not the applicant's achievement, that must establish the obviousness of the combination.

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[1] MPEP §2142, *citing In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

The teachings of the references, their relatedness to the field of the applicant's endeavor, and the knowledge of persons of ordinary skill in the field of the invention, are all relevant considerations. See *In re Oetiker*, 977 F.2d at 1447, 24 USPQ2d at 1445-46; *In re Gorman*, 933 F.2d at 986-87, 18 USPQ2d at 1888; *In re Young*, 927 F.2d 588, 591, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991). When the references are in the same field as that of the applicant's invention, knowledge thereof is presumed. However, the test of whether it would have been obvious to select specific teachings and combine them, as did the applicant, must still be met by identification of some suggestion, teaching, or motivation in the prior art, arising from what the prior art would have taught a person of ordinary skill in the field of the invention. *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596,1600 (Fed. Cir. 1988).

The Office Has Not Established A *Prima Facie* Case Of Obviousness

The Office has not established a *prima facie* case of obviousness because not all of the three necessary criteria have been met. Therefore, as discussed *infra*, the pending claims are patentable over the cited references.

Applicants' Invention

The present invention as shown in independent claims 1, 9, 34, 55 and 56 provides methods for inhibiting or reducing rejection of a solid organ or tissue/cellular transplant in a subject comprising the following sequence of steps: administering T cell depleted bone marrow cells to the subject before, during or after the solid organ or tissue/cellular transplant; administering an alkylating agent (e.g., busulfan) to the subject in an amount that facilitates mixed chimerism; administering a subsequent dose of T cell depleted bone marrow. Additionally, an immunosuppressive composition that blocks T cell

costimulatory signals can be administered in the subject before, during or after the transplant.

Also, the present invention as shown in independent claims 62 and 63 provides methods for inhibiting or reducing rejection of solid organ or tissue/cellular transplant in a subject comprising administering: two doses of T cell depleted bone marrow, an immunosuppressive composition that blocks T cell costimulatory signals, and an alkylating agent at specific dosages.

A Discussion of the References Cited by the Office

Sykes, U.S. Patent No. 6,514,513 ('513)

Sykes discloses a method of promoting graft acceptance (e.g. skin graft), by a recipient mammal, wherein the graft is from a donor mammal of a second species. The method includes: administering to the recipient, an inhibitor, (e.g. either CTLA4Ig or anti-CD40 ligand mAB); administering low dose whole body irradiation; introducing hematopoietic stem cells (e.g., a bone marrow preparation) into the recipient mammal; and preferably, implanting the graft in the recipient. The hematopoietic cells are believed to prepare the recipient for the graft that follows, by inducing tolerance at both the B-cell and T-cell levels (Sykes at column 1, lines 49-52).

Sykes uses irradiation in the methods described (Sykes at column 22, lines 36-40; column 23, lines 15-19; column 24, lines 34-36; column 25, lines 9-12; and column 27, lines 52-55) but also suggests that busulfan may be used in lieu of irradiation, to create hematopoietic space. However, this suggestion is merely a wish. There is no reasonable expectation of success if busulfan is substituted for whole body irradiation. This is because there is no direct correlation between the irradiation dosage and the busulfan

dosage administered, to facilitate mixed hematopoietic chimerism. In fact, Hassan et al., discussed *infra*, teach that total body irradiation is superior to busulfan in terms of patient survival.

Sykes fails to teach the use of busulfan together with other agents of the claimed methods for facilitating mixed hematopoietic chimerism, and the effective dosage of busulfan for such use. Additionally, Sykes fails to teach the therapeutic sequence of the claimed invention as disclosed in independent claims 1, 9, 34, 55 and 56. The claimed methods requires: T cell depleted bone marrow administered to a subject; an alkylating agent administered to a subject after the bone marrow; additional T cell depleted bone marrow administered to a subject after the alkylating agent.

The combination of Sykes and the additional references (discussed infra) cited by the Office does not rectify the deficiencies in Sykes and does not render the claimed invention obvious.

Andersson et al., U.S Patent Nos. 5,430,057 ('057) and. 5,559,148 ('148)

Patents '057 and '148 have identical disclosures, since the '148 patent is a continuation of the '057 patent. Accordingly, the '057 and the '148 patents are discussed together herein. The '057 and the '148 patents provide methods for use of parenteral formulation of busulfan, in the clinical treatment of human neoplasms, with therapy based on parenteral preparation alone, or in combination with other cytotoxic agent(s). Additionally, these patents provide formulations to increase solubility of busulfan, design of a chemically stable formulation of busulfan that is suitable for parenteral administration, and techniques to extract busulfan from blood, as well as pharmacokinetics of commercially available busulfan, and busulfan when solubilized in polyethylene glycol.

The '057 and the '148 patents fail to teach what the primary reference fails to teach, namely, the use of busulfan together with other agents of the claimed methods for facilitating mixed hematopoietic chimerism, and the effective dosage of busulfan for such use. Moreover, these patents fail to teach or suggest the use of busulfan for inhibition or reduction of rejection of solid organ transplants. Accordingly, the combination of the Sykes and the '057 and '148 patents does not render obvious the claimed methods.

Slattery et al., Therapeutic Drug Monitoring, 1998, 20:543-549

Slattery et al. provide methods for use of busulfan, to ablate marrow before hematopoietic stem cell transplantation, and the use of high levels of busulfan, in combination with cyclophosphamide, to treat patients with chronic myeloid leukemia. Further, Slattery et al. state that the therapeutic window for busulfan is narrow, and disease and graft-source dependent.

Slattery et al. fail to teach what the primary reference fails to teach, namely, the use of busulfan together with other agents of the claimed methods, for facilitating mixed hematopoietic chimerism, and the effective dosage of busulfan for such use. Further, Slattery et al. do not teach or suggest the use of busulfan for inhibition or reduction of rejection of solid organ transplants. Accordingly, the combination of the Sykes and Slattery et al. does not render obvious the claimed methods.

Hassan et al., Blood, 1994, 84:2144-2150

Hassan et al. provides methods for use of busulfan in patients only undergoing bone marrow transplantation and evaluates the bioavailability of busulfan. Additionally, Hassan et al. note that although busulfan has been introduced as an alternative to total body irradiation (TBI), TBI treatment of patients conferred a survival advantage over

busulfan treated patients (page 1, column 1, paragraph 2).

Hassan et al. teach that busulfan has a higher mortality rate compared to TBI. Accordingly, Hassan et al. teach away from the claimed methods. In view of teaching of Hassan et al., the combination of references cited by the Office in its rejection of the claims fail to render the claimed methods obvious.

The Merck Manual of Diagnosis and Therapy, 17th Ed., edited by Beers et al., 1999

The Merck Manual (pages 1067-1074) teaches an overview of biology related to transplantation including the immunobiology of rejection, components of tissue compatibility and immunosuppression. Immunosuppressive drugs mentioned in the Merck Manual include corticosteroids, azathioprine, cyclophosphamide, cyclosporine and tacrolimus. Other immunosuppressive factors mentioned in the Merck Manual include monoclonal antibodies and irradiation.

The Merck Manual fails to teach what the primary reference ('513) fails to teach, namely, the use of busulfan together with other agents of the claimed methods, for facilitating mixed hematopoietic chimerism, and the effective dosage of busulfan for such use. Further, the Merck Manual does not teach or suggest the use of busulfan for inhibition or reduction of rejection of solid organ transplants. Accordingly, the combination of the '513 and the Merck Manual references does not render obvious the claimed methods.

Shichi et al., U.S. Patent No. 4,843,092

Shichi et al. teach an immunosuppressive agent comprising macrolide antibiotic(s) for suppressing rejection after organ transplantation and as an agent for treating immune diseases. The background section of Shichi et al. mentions that "[a]s immunosuppressive

agents, there are known alkylating agents such cyclophosphamide" which can be used as agents for suppressing rejection which may occur after transplantation. Shichi et al. does not teach how to use cyclophosphamide (e.g. does not teach any methods of administration nor any dosages by itself or in combination with other agents) much less teach the use of busulfan.

Shichi et al. fail to teach what the primary reference ('513) fails to teach, namely, the use of busulfan together with other agents of the claimed methods, for facilitating mixed hematopoietic chimerism, and the effective dosage of busulfan for such use. Further, Shichi et al. do not teach or suggest the use of busulfan for inhibition or reduction of rejection of solid organ transplants. Accordingly, the combination of the '513 and Shichi et al. references does not render obvious the claimed methods.

Strom et al., Therapeutic Immunology edited by Austen et al., 1996

Strom et al. teach the use of multiple agents simultaneously, with each agent directed at a different molecular target, for immunosuppressive therapy. The agents cited by Strom et al. to be used in combination are: cyclosporine, tacrolimus (FK506), corticosteroids, azathioprine, mycophenolate mofetil, OKT3 monoclonal antibody, anti-IL-2 antibody, anti-IL-2 receptor antibody, anti-adhesion molecule antibody and rapamycin.

Strom et al. fail to teach what the primary reference fails to teach, namely, the use of busulfan together with other agents of the claimed methods for facilitating mixed hematopoietic chimerism and tolerance induction, and the effective dosage of busulfan for such use. Moreover, Strom et al. fail to teach or suggest the use of busulfan for inhibition or reduction of rejection of solid organ transplants. Accordingly, the combination of the Sykes and the Strom et al. does not render obvious the claimed methods.

Sykes et al., Nature Medicine 3:783-787, 1997

Sykes et al. teach donor specific T-cell tolerance induced by administering to a murine subject: 1) depleting anti-CD4 and anti-CD8 monoclonal antibodies to remove the host immune barriers to T cell allo-engraftment, 2) local thymic irradiation to produce space in the thymic compartment, and 3) a high dose of MHC-mismatched bone marrow cells. Sykes et al. fail to teach what the primary reference ('513) fails to teach, namely, the use of busulfan together with other agents of the claimed methods, for facilitating mixed hematopoietic chimerism, and the effective dosage of busulfan for such use. Sykes et al. do not teach or suggest the use of busulfan for inhibition or reduction of rejection of solid organ transplants. Accordingly, the combination of the '513 and Sykes et al., references does not render obvious the claimed methods.

Wekerle et al., J Exp Med, 187:2037-2044, 1998

Wekerle et al. teach induction of transplantation tolerance by administering to a murine subject: 1) single injections of anti-CD40 ligand antibody and CTLA4Ig, 2) whole bod irradiation, and 3) MHC-mismatched allogeneic bone marrow transplantation.

However, Wekerle et al. fail to teach what the primary reference ('513) fails to teach, namely, the use of busulfan, together with other agents of the claimed methods, for facilitating mixed hematopoietic chimerism, and the effective dosage of busulfan for such use. Moreover, Wekerle et al. fail to teach or suggest the use of busulfan for inhibition or reduction of rejection of solid organ transplants. Accordingly, the combination of the '513 and Wekerle et al. references, does not render obvious the claimed methods.

THE LEGAL STANDARD HAS NOT BEEN MET BY THE OFFICE

The references in combination do not teach all of the claimed steps

The Office asserts that the claimed method is an obvious modification of the Sykes reference. However, as discussed *supra*, the prior art references in combination does not teach or suggest all of the claim limitations, in the order claimed, namely, steps a-d of claims 1, 9, 34, 55, 56, 62 or 63.

Moreover, Hassan et al. teach away from the claimed method. Thus the combination of the prior art references does not render obvious the claimed method.

There was no suggestion to modify the prior art in order to obtain the claimed invention.

The Office's statement that it was within the skill in the art to make the modifications necessary to advance from the prior art to the claimed method is similar to an erroneous statement made in *Ex parte Levengood.*[2] In *Levengood,* the examiner stated that because the various aspects of the claimed process were individually known in the art (in the instant case, this is not true), the modifications of a prior art process necessary to arrive at the claimed invention were "well within the ordinary skill of the art at the time the claimed invention was made."[3]

The Board of Patent Appeals and Interferences reversed the examiner's rejection because it was based on the wrong standard of obviousness: "At best, the examiner's comments regarding obviousness amount to an assertion that one of ordinary skill in the relevant art would have been able to arrive at appellant's invention because he had the necessary skills

[2] 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993).

to carry out the requisite process steps. This is an inappropriate standard for obviousness. . . . That which is within the capabilities of one skilled in the art is not synonymous with obviousness."[4]

The Office's current reliance on what was within the skill in the art to support the obviousness of the modifications separating the prior art from the claimed invention is likewise an erroneous basis for finding the invention *prima facie* obvious over the cited art.

To establish a *prima facie* case of obviousness, the Office must present evidence that one skilled in the art would have been led to arrive at the claimed invention.[5] Mere unsupported arguments cannot take the place of evidence.[6]

In this regard, Sykes merely suggests that other methods of creating hematopoietic space, e.g., administering hematopoietic space creating antibodies or drugs, e.g., cyclophasmide or busulfan, to the recipient, can be used (513 patent at column 5, lines 3-5). Without more, this statement cannot suggest the claimed invention. Merely desiring an end result does not constitute a specific modification of the prior art.

There is no evidence that any modification of the prior art would have led to a reasonable expectation of success in practicing the claimed invention.

It would not be enough to imply that, given the capabilities of those skilled in the art, it would have been obvious to try the claimed invention. In *In re O'Farrell,* the Federal Circuit gave examples of what would be obvious to try, but not obvious under 35 U.S.C.

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[3] *Id.* at *1301.*
[4] *Id.* (citations omitted).
[5] *Id.*
[6] In re Wiseman, 596 F.2d 1019, 201 USPQ 658, 661 (CCPA 1979).

§103: "to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it."[7] *O'Farrell* clarified the additional requirement for a reasonable expectation of success.

Sykes provides only a cursory statement of replacing irradiation with busulfan as a preparative regimen for bone marrow transplants (BMT). This is very different from the claimed methods of inhibiting solid organ transplants. None of the cited references, alone, or in combination, provides guidance for modifying the methods to achieve therapeutically effective methods as claimed. In fact, Hassan et al. teach that total body irradiation is superior to busulfan in terms of patient survival. Moreover, there was no reason to believe that busulfan dosages of the art as a preparative regimen for BMT would be extrapolatable for busulfan dosages for facilitating MHC in connection with solid organ transplants. Such cursory statements are not equivalent to a reasonable expectation of success because there was no direction or guidance on how to proceed to achieve the prophetic goal based on the references.

Additionally, Sykes does not teach any therapeutic sequence. The claimed method requires: administration of T cell depleted bone marrow to a subject; administration of an alkylating agent after the T cell depleted bone marrow to a subject; administration of additional T cell depleted bone marrow after the alkylating agent to a subject.

Sykes fails to teach the use of busulfan together with other agents of the claimed methods for facilitating mixed hematopoietic chimerism, and the effective dosage of busulfan for such use. Additionally, Sykes fails to teach the therapeutic sequence of the claimed method.

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[7] 853 F.2d 894, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

In *In re Gangadharam,* the Federal Circuit reversed an obviousness rejection maintained by the Board of Patent Appeals and Interferences on the basis of a single prior art reference because the Patent and Trademark Office (PTO) had failed to meet its burden of proving a *prima facie* case of obviousness.[8] The single cited reference stated that the result reported therein "offers a hopeful lead" for the therapeutic use claimed in the later application. The Federal Circuit stated that the Board's attempt to base their finding of a reasonable expectation of success for the claimed use on the one prior art reference "fell woefully short of its burden."[9]

As in *Gangadharam,* the Office in the present case is basing the rejection under Section 103, of the claimed methods on the hopeful lead provided by the prior art. Like *Gangadharam,* the Office's attempt to base an obviousness rejection on the cited reference, i.e. *Sykes,* falls woefully short of its burden because data using irradiation as a preparative regimen cannot teach the claimed method, for inhibiting rejection of a solid organ transplant in a subject. In fact, art cited by the Office teaches that radiation treatment is not equivalent to busulfan treatment (Hassan et al.).

The Office has not provided evidence that the prior art teaches or suggests *as a whole* the claimed methods. The claimed methods cannot be obvious over the cited references, because there was no suggestion regarding how to modify the prior art, in order to achieve the claimed methods. Moreover, even if it were obvious to try the combination of elements claimed, much less the specified sequence of administering the elements, without a reasonable expectation of success, a *prima facie* case of obviousness cannot be made. It is therefore, respectfully requested that the rejection under 35 U.S.C. §103, be withdrawn, and that the claims be allowed.

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[8] 889 F.2d 1101, 13 USPQ2d 1568 (Fed. Cir. 1989).
[9] *Id.* at 1569.

THE CLAIMED INVENTION POSSESSES UNEXPECTED ADVANTAGES THAT THE CITED REFERENCES DOES NOT TEACH

Applicants respectfully contend that the cited references do not render the claimed invention *prima facie* obvious. Furthermore, the alleged obviousness is rebutted by evidence of unexpected properties of the claimed invention (*In re Davies and Hopkins*, 475 F.2d 667, 177 U.S.P.Q. 381 (1973)).

In addition to Applicants' previous showing, Applicants provide post filing confirmatory data showing that the methods of the invention possess superior properties. Specifically, Applicants provide the following:

1. Exhibit 1: L. Kean et al.

   Here the authors show that nonmyeloablative preconditioning with busulfan (20mg/kg) coupled with costimulation blockade (CTLA4-Ig and anti-CD40L) can safely produce stable white blood cell (WBC) mixed chimerism and total replacement of the peripheral red cell compartment, resulting in a phenotypic cure of murine SCD. Furthermore, this cure is accomplished with fully major histocompatibility complex (MHC) mismatched donor marrow. Importantly, the hematologic cure that occurred with total replacement of the red cell compartment was accompanied by normalization of characteristic sickle organ pathology, indicating a total-body amelioration of disease.

2. Exhibit 2: Z. Guo et al.

The results of these studies demonstrate that the infusion of donor bone marrow together with busulfan and costimulation blockade (anti-CD40L mAb and CTLA4-Ig) induces hematopoietic chimerism and promotes the long-term survival of intestinal allografts transplanted into mice that have completed the treatment regimen. This long-term survival is associated with donor-specific hyporesponsiveness in vitro and deletion of donor-reactive T cells in vivo.

3. Exhibit 3: N. Shirasugi et al.

Treatment regimens consisting of costimulation bloackade CB alone (CTLA4-Ig and anti-CD40L), CB and donor bone marrow cells (BMCs), and CB and donor splenocytes (DST) promote long-term allograft survival, but do not confer robust tolerance nor prevent chronic rejection in the face of a rechallenge with a donor skin graft. In contrast, a regimen consisting of CTLA4-Ig, anti-CD40L, donor BMCs, and a minimally myelosuppressive dose of busulfan produced stable donor-specific tolerance, and prevented both early and late cellular infiltration and chronic allograft vasculopathy, despite the rigorous rechallenge of a donor skin graft.

In view of the aforementioned discussion, Applicants respectfully request that the Patent Office reconsider and withdraw the rejection of the claims, under 35 U.S.C. §103.

ITEM 12: REJECTION UNDER 35 U.S.C. §103(a)

The Office rejects Claims 1, 9 and 33, under 35 U.S.C §103(a), as allegedly unpatentable over Sykes et al. (U.S. Patent No. 6,514,513), in view of art known practice and modes of administration of alkylating agents such as busulfan/cyclophosmide at various times to meet the needs of the patient, as acknowledged on pages 26-27 of the instant specification and as evidenced by Andersson et al. (U.S Patent Nos. 5,430,057 and 5,559,148), Slattery et al. (Therapeutic Drug Monitoring, 1998, 20:543-549), Hassan et al. (Blood 84,2144-2150), The Merck Manual of Diagnosis and Therapy, 17th Ed. (edited by Beers et al.), Shichi et al. (U.S. Patent No. 4,843,092), Strom et al. (Therapeutic Immunology edited by Austen et al.), Sykes et al. (Nature Medicine 3:783-787, 1997) and Wekerle et al. (J Exp Med, 187:2037-2044, 1998) and in view of Larsen et al. (US Patent No. 5,916,560).

Applicants respectfully disagree.

Sykes et al. (U.S. Patent No. 6,514,513), Andersson et al., Slattery et al., Hassan et al., The Merck Manual of Diagnosis and Therapy, 17th Ed., Shichi et al., Strom et al., Sykes et al. (Nature Medicine 3:783-787, 1997) and Wekerle et al. were discussed *supra*.

Larsen et al. (Larsen) teaches compositions and methods of inhibiting an immune response by using a combination of two agents, wherein the first agent blocks the CTLA4/CD28/B7 pathway, and the second agent blocks the gp39/CD40 pathway.

Larsen fails to teach what the primary reference, Sykes et al. (U.S. Patent No. 6,514,513), fails to teach, namely, any amount of busulfan that would facilitate mixed hematopoietic chimerism. Larsen does not teach the therapeutic sequence of the claimed method. Further, Larsen does not teach or suggest the use of busulfan for inhibition or reduction of rejection of solid organ transplants. Therefore, the combination of Sykes (U.S. Patent

No. 6,514,513) and Larsen does not render obvious the claimed methods. Accordingly, Applicants respectfully request that the rejection be withdrawn.

ITEM 13: REJECTION UNDER 35 U.S.C. §103(a)

The Office rejects claims 1, 5, 6, 9, 10, 12-23, 30, 34, 36-37, 44-52, 54-60, 62-63 and 64-74 under 35 U.S.C §103(a) as allegedly unpatentable, over Sykes et al. (U.S. Patent No. 6,514,513), in view of art known practice and modes of administration of alkylating agents such as busulfan/cyclophosmide at various times to meet the needs of the patient, as acknowledged on pages 26-27 of the instant specification and as evidenced by Andersson et al. (U.S Patent Nos. 5,430,057 and 5,559,148), Slattery et al. (Therapeutic Drug Monitoring, 1998, 20:543-549), Hassan et al. (Blood 84,2144-2150), The Merck Manual of Diagnosis and Therapy, 17th Ed. (edited by Beers et al.), Shichi et al. (U.S. Patent No. 4,843,092), Strom et al. (Therapeutic Immunology edited by Austen et al.), Sykes et al. (Nature Medicine 3:783-787, 1997) and Wekerle et al. (J Exp Med, 187:2037-2044, 1998) and in view of Peach et al. (US 20020182211) (Peach).

Applicants respectfully disagree.

Sykes et al. (U.S. Patent No. 6,514,513), Andersson et al., Slattery et al., Hassan et al., The Merck Manual of Diagnosis and Therapy, 17th Ed., Shichi et al., Strom et al., Sykes et al. (Nature Medicine 3:783-787, 1997) and Wekerle et al. were discussed *supra*.

Peach teaches CTLA4 mutant molecules with mutations at position 29, and at position 104.

Peach fails to teach what the primary reference fails to teach, namely, any effective amount of busulfan that facilitates mixed hematopoietic chimerism. Peach does not teach

the therapeutic sequence of the claimed method. Further, Peach does not teach or suggest the use of busulfan for inhibition or reduction of rejection of solid organ transplants. Therefore, the combination of the Sykes et al. (U.S. Patent No. 6,514,513) and Peach, does not render obvious the claimed methods. Accordingly, Applicants respectfully request that the rejection be withdrawn.

ITEM 14: NO CLAIMS ALLOWED

The Office has indicated that no claims have been allowed in the instant application. However, Applicants respectfully request that the Patent Office reconsider and withdraw the rejections of the claims for the reasons specified *supra*.

ITEM 15: INQUIRIES

The Office indicated that any inquiries concerning this communication or earlier communications should be directed to Philip Gambel. Further, if attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Chan can be reached.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, Applicants undersigned attorney invites the Office to telephone her at the number provided below.

No other fee is deemed necessary in connection with the filing of this Amendment. If any fee is necessary, the Patent Office is authorized to charge any additional fee to Deposit Account No. 50-0306.

Respectfully submitted,

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